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Association Between *PTPN22* Polymorphisms and IgE Responses to Staphylococcal Superantigens in Chronic Urticaria

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Protein tyrosine phosphatase-22 (*PTPN22*) gene encodes lymphoid-specific tyrosine phosphatase (Lyp), an inhibitor of T cell activation. A polymorphism of the *PTPN22* gene has been found to be associated with chronic urticaria (CU). We investigated the associations between *PTPN22* gene polymorphisms and CU characteristics, including serum specific IgE antibodies response to toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxin A (SEA). CU patients (n=409) and normal healthy controls (n=388) were enrolled in the present study. Serum specific IgE to TSST-1 and SEA were measured by ImmunoCAP®. Five *PTPN22* single nucleotide polymorphisms, -1123G>C, 1858C>T, 13145A>G, 14943C>T, and 20628A>G, were genotyped. There were no significant differences in genotype or haplotype frequencies of these polymorphisms between the 2 groups. CU patients carrying the GG genotype at 20628A>G ($P=0.035$) or haplotype 3 [GGG] ($P=0.047$) had a significantly higher prevalence of serum specific IgE to TSST-1 compared to non-carriers. Similarly, CT/TT genotype at 14943C>T had a significantly higher prevalence of serum specific IgE to SEA ($P=0.045$). The findings suggest that the *PTPN22* gene polymorphisms at 20628A>G and 14943C>T may enhance serum specific IgE responses to TSST-1 and SEA, which may contribute to CU pathogenesis.

Key Words: Chronic urticaria; polymorphisms; *PTPN22*; staphylococcal enterotoxin

INTRODUCTION

Chronic urticaria (CU) is characterized by pruritic wheals that last several hours and recur for more than 6 weeks.[1] It is a common and potentially debilitating skin condition that affects up to 1% of the general population with variable duration, from several months, to decades.[2] The symptoms are instigated by activated mast cells and their subsequent release of histamine and other proinflammatory mediators.[3] The underlying causes and mechanisms of mast cell activation in CU remain to be identified. Functional autoantibodies against the high-affinity immunoglobulin E receptor (FcεRI) or immunoglobulin E (IgE) found in a subset of CU patients can activate and degranulate mast cells; however, the absence of autoantibodies in other CU populations indicate other potential causes of CU.[4]

Recently, protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*), a strong susceptible gene for various autoimmune diseases, is found to be associated with CU.[5] *PTPN22* gene is located on chromosome 1p13.3-p13.1 and encodes the lymphoid protein tyrosine phosphatase (Lyp) which is a negative regulator of T-cell antigen receptor (TCR) signaling.[6] *PTPN22* gene polymorphism (1858C>T) impairs T-cell signaling and may influence autoimmune mechanisms and promote proinflammatory responses.[7] Additionally, a correlation has been found between T-cell activation and mast cell degranulation in CU patients that indicate the role of T cells in CU pathogenesis.[8]

Superantigens are exotoxins produced by microorganisms that can activate a widerange of T cells.[9] Superantigens, particularly produced by *Staphylococcus aureus* (SA), such as staphylococcal enterotoxins (SE) A, SEB, and toxic shock syndrome toxin-1 (TSST-1), have been associated with various inflammatory diseases, such as atopic dermatitis (AD), asthma and psoriasis.[10-12] Staphylococcal superantigens can activate T cells that result in the production of IgE and IgG antibodies from B cells.[13] In addition, staphylococcal superantigens have been shown to induce inflammation via the production of serum specific IgE to superantigens in patients with AD.[14] Specific IgE antibodies

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are of functional relevance because they can trigger a mediator release from sensitized basophils.[15]

We hypothesize that *PTPN22* variants promote the generation of specific IgE to staphylococcal superantigens via T cell activation, which might play an important role in the pathogenesis of CU. To investigate the role of *PTPN22* gene polymorphisms in CU and its association with specific IgE responses to staphylococcal superantigens, we genotyped 5 single nucleotide polymorphisms (SNPs) of the *PTPN22* gene of CU patients and analyzed their associations with clinical characteristics.

MATERIALS AND METHODS

We enrolled 409 Korean CU patients and 388 normal healthy controls (NC) who had no history of urticaria symptoms in the present study from the Department of Allergy and Clinical Immunology, Ajou University Hospital, Suwon, Korea. Written informed consent was obtained from each subject, and approved by the institutional review board of Ajou University Hospital. Skinprick tests were performed with 55 common aeroallergens (Bencard, West Sussex, UK), and atopy was defined as 1 or more positive reactions to common inhalant allergens. Total IgE concentrations and serum specific IgE to staphylococcal superantigens, TSST-1, SEA, and SEB were measured using ImmunoCAP® (Thermo Scientific, Uppsala, Sweden) according to the manufacturer's instructions. Intradermal autologous serum skin tests (ASSTs) were performed following the method used by the EAACI/GA^{2}LEN task force consensus report.[16] A serum-induced wheal diameter greater than 1.5 mm of a control induced by saline at 30 minutes was accepted as positive. Serum specific IgG to thyroglobulin (TG) and thyroperoxidase (TPO) were detected by radioimmunoassay (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany). Serum antinuclear antibodies (ANA) were measured by enzyme linked immunosorbent assay using commercially available kits (BL-Diagnostika GmbH, Mainz, Germany), according to the manufacturer's instructions.

Genomic DNA was isolated from the peripheral blood using PUREGENE® DNA purification kit (Gentra systems Inc., MN, USA). We selected five SNPs of the *PTPN22* gene, one in promoter (-1123G>C), one in exon (1858C>T) and three in intron (13145A>G, 14943C>T and 20628A>G), based on previous reported studies and direct sequencing in the promoter region. Genotyping was performed by a primer extension method and the SNaPshot ddNTP primer extension kit (Applied Biosystems, Foster City, CA, USA). Table 1 lists the amplification and extension primers used for genotyping. Three haplotypes (ht) were constructed from the combination of the three gene variants, -1123G>C, 20628A>G and 13145A>G using Haploview 4.2.

Statistical analysis was performed using IBM SPSS Statistics version 20 for Windows (SPSS Inc., Chicago, IL, USA). A Chi-square test was used to detect a significant departure in genotype frequency from the Hardy-Weinberg equilibrium at each SNP. Differences in genotype and haplotype frequencies between the 2 groups were examined by logistic regression analysis in codominant, dominant, and recessive models after accounting for age and sex as covariables. Differences in the mean values of phenotypic characteristics between the 2 groups were compared by analysis with Chi-square test for categorical variables and independent t test for continuous variables. Statistical significance levels of all analyses were set at $P<0.05$.

Table 1. The amplifying and extension primers for SNP genotyping

Locus (SNP ID)		Primers
-1123G>C	Forward	tcccagttttcttcaggatca
(rs2488457)	Reverse	ggagcacctgaccagacagt
Promoter	Genotyping	ttgtacccattgagaggttatgcaagct
13145A>G	Forward	tcccaaatcatcctccagaa
(rs1217418)	Reverse	tgattatgccactgcactcc
Intron 3	Genotyping	gaacagaaattacacggggtgactaca
14943C>T	Forward	gtctaacccctttgggcttc
(rs11582409)	Reverse	tgttgccattctgagttgaca
Intron 5	Genotyping	ctactttttcagactcccaggaagtct
20628A>G	Forward	ggctaggagaagggaagagc
(rs1217407)	Reverse	ctccagcctgggtaacagag
Intron 10	Genotyping	tatgggtattctggggtaggttaaaag
1858C>T	Forward	gagtgcagtggcacaatcat
(rs2476601)	Reverse	ggatagcaactgctccaagg
Exon 14	Genotyping	tcaaccacaataaatgattcaggtgtcc

RESULTS

The mean age was significantly higher in CU patients compared to normal control subjects (39.59 ± 11.53 vs 29.64 ± 9.70 years, $P<0.001$). CU patients exhibited a significantly higher atopy rate (48.8% vs 24.3%, $P<0.001$) and a higher serum total IgE level (265.82 ± 436.33 vs 76.91 ± 133.28 IU/mL, $P<0.001$) than normal control subjects. CU patients had a significantly higher prevalence of serum specific IgE to TSST-1 (26.7% vs 12.2%, $P<0.001$) and serum specific IgE to SEB (21.3% vs 6.3%, $P<0.001$) compared to normal control subjects (Table 2), while serum specific IgE to SEA tended to be higher in CU patients. The genotype and haplotype frequencies of all SNPs did not differ significantly between CU patients and normal control subjects based on logistic regression analysis (Table 3).

When clinical parameters were compared according to the genotype, CU patients with the GG homozygous genotype at 20628A>G exhibited a significantly higher prevalence of serum specific IgE to TSST-1 than those with the AA/AG genotype (45.5% vs 24.3%, $P=0.035$, Figure. A). In addition, the ht3 [GGG] carrier showed a significantly higher prevalence of serum specific IgE to TSST-1 compared to noncarriers in CU patients (47.1 vs 24.7%, $P=0.047$; Figure. B). Similarly, the CT/TT genotype at

14943C>T was associated with a significantly higher prevalence of serum specific IgE to SEA compared to the CC genotype (16.7% vs 6.6%, $P=0.045$; Figure. C). We analyzed *PTPN22* SNPs in association with various autoantibodies, such as serum specific IgG to TG, serum specific IgG to TPO, and ANA in CU patients; however, no significant association was found. We also analyzed the prevalence of human leukocyte antigens (HLA) allele: DRB1*1302 and DQB1*0609 which were reported as significant HLA alleles associated with aspirin-intolerant CU according to *PTPN22* gene polymorphism in CU patients but did not find significant relations between them (data not shown).[17]

Table 2. Clinical characteristics of the study subjects

	CU (n=409)	NC (n=388)	*P* value
Age (year)	39.59±11.53	29.64±9.7	<0.001
Sex (male, %)	162/396 (40.9%)	167/351 (47.6%)	0.067
Atopy (positive/total)	177/363 (48.8%)	55/226 (24.3%)	<0.001
Total IgE (IU/mL)	265.82±436.33	76.91±133.28	<0.001
ASST (positive/total)	35/49 (71.4%)	NA	NA
C3 (mg/dL)	118.62±25.92	NA	NA
C4 (mg/dL)	28.94±9.79	NA	NA
ANA (positive/total)	31/205 (15.10%)	23/118 (19.50%)	0.311
TG-specific IgG (positive/total)	42/200 (21.0%)	21/105 (20.0%)	0.838
TPO-specific IgG (positive/total)	27/202 (13.4%)	12/108 (11.10%)	0.568
TSST-1-specific IgE (positive/total)	51/191 (26.7%)	22/180 (12.2%)	<0.001
SEA-specific IgE (positive/total)	16/160 (10.0%)	10/163 (6.1%)	0.202
SEB-specific IgE (positive/total)	34/160 (21.3%)	10/160 (6.3%)	<0.001

P value was calculated using Chi-Square test for categorical variables and independent *t*-test for continuous variables.
ANA, anti-nuclear antibody; ASST, autologous serum skin test; C3, complement 3; C4, complement 4; NA, not assessable; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TG, thyroglobulin; TPO, thyroperoxidase; TSST, toxic shock syndrome toxin.

DISCUSSION

PTPN22 polymorphism and staphylococcal superantigens have been independently associated with various chronic skin

Table 3. Genotype frequencies of PTPN22 polymorphism distributed in 2 study groups

Loci	Genotype	CU (n=409)	NC (n=388)	*P* value
-1123G>C	CC	175 (42.8%)	161 (41.5%)	0.354
(rs2488457)	CG	183 (44.7%)	186 (47.9%)	0.682
	GG	51 (12.5%)	41 (10.6%)	0.231
13145A>G	AA	304 (74.3%)	293 (75.5%)	0.909
(rs1217418)	GA	97 (23.7%)	87 (22.4%)	0.834
	GG	8 (2.0%)	8 (2.1%)	0.751
14943C>T	CC	276 (67.5%)	246 (63.4%)	0.468
(rs11582409)	CT	130 (31.8%)	141 (36.3%)	0.554
	TT	3 (0.7%)	1 (0.3%)	0.307
20628A>G	AA	178 (43.5%)	168 (43.3%)	0.256
(rs1217407)	GA	182 (44.5%)	185 (47.7%)	0.207
	GG	49 (12.0%)	35 (9.0%)	0.506

Each *P* value was calculated with co-dominant, dominant and recessive models. Logistic regression analysis was applied to control for age and sex as covariables.
CU, chronic urticaria; NC, normal control; n, number of subjects.

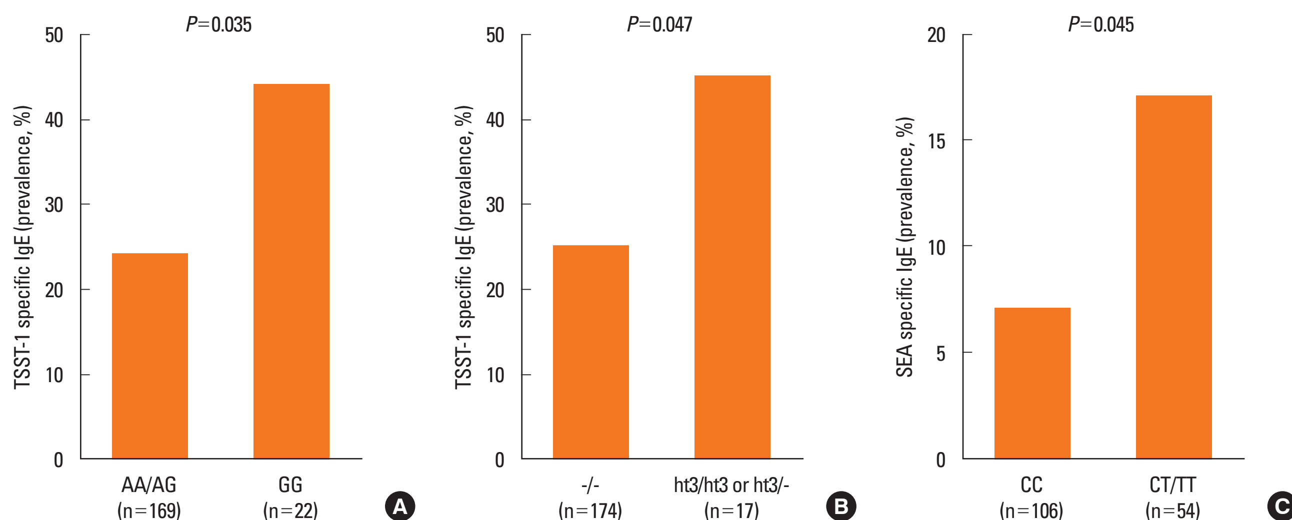

Figure. Comparison of clinical parameters according to genotype and haplotype of the *PTPN22* polymorphisms in CU patients. (A) Prevalence of serum specific IgE to TSST-1 according to the 20628A>G polymorphism. (B) Prevalence of serum specific IgE to TSST-1 according to the haplotype 3 [GGG]. (C) Prevalence of serum specific IgE to SEA according to the 14943C>T polymorphism.

inflammatory diseases, including CU; however, their mutual role in the pathogenesis of CU has not been studied.[5,18] Here, we attempted to find an association between these 2 factors in CU pathogenesis. We found significant associations of 2 intronic SNPs, 20628A>G and 14943C>T, with the prevalence of serum specific IgE against staphylococcal superantigens, TSST-1 and SEA, respectively in CU patients.

PTPN22 encodes for LYP, a protein tyrosine phosphatase, which is considered a powerful inhibitor of T-cell activation.[19] Brzoza *et al.*[5] recently reported that a promoter SNP, -1123G>C, was associated with CU susceptibility in a Polish population, which was not observed in the present study. The prevalence of C allele was higher than G allele in our study group, suggesting that ethnic differences might play important role in the polymorphism. The SNP 1858C>T is the most prevalent polymorphism in a European population and has been associated with various autoimmune diseases.[20] However, no polymorphism was found in the present study subjects, which is consistent with previously published studies conducted in a Korean population.[6]

In various skin inflammatory diseases, including atopic dermatitis, superantigens are considered probable causative factors that elicit mast cell degranulation.[21] We also previously demonstrated a high prevalence of serum specific IgE to staphylococcal superantigens in CU patients that indicated a role of staphylococcal superantigens in CU pathogenesis.[18] The present study found that both 20628A>G and 14943C>T were associated with a higher prevalence of serum specific IgE to staphylococcal superantigens, indicating that superantigens and *PTPN22* together can play important role in CU pathogenesis. To date, there has been no reported evidence of functional effect of the two intronic SNPs. Due to their location in the intron, these variants may not be functional but may be in allelic association with functional variants in a promoter or enhancer element of the *PTPN22* gene that results in reduced *PTPN22* gene expression. As *PTPN22* regulate negative activation of T cells, diminished activity of *PTPN22* results in hyperresponsiveness of T-cell promoting proinflammatory T-cell responses.[22,23] Released cytokines from activated T cells can stimulate B cells to produce specific antibodies.[24] In polymorphic *PTPN22* whose activity is diminished, T cells might release higher levels of cytokines which can activate B cells more intensely and result in the increased production of specific IgE against staphylococcal superantigens from B cells.[23] *In vivo* data have shown that mice lacking *PEP* (*PTPN22* ortholog of mice) has increased effector/memory T-cell pool and germinal layers along with an increased serum IgE level.[25] Consequently, the enhanced synthesis of serum specific IgE against superantigens due to polymorphic *PTPN22* could activate dermal mast cells to release histamine. Jabara *et al.*[26] demonstrated that TSST-1 can modulate the activity of T cells and augment the synthesis of IgE from B cells. The results suggest that *PTPN22* gene polymorphism alters the activity of T cells and contributes to enhanced serum specific IgE responses against staphylococcal superantigens.

Leung *et al.*[27] demonstrated that 57% of all atopic dermatitis patients have circulating IgE to staphylococcal enterotoxins, and these enterotoxins could degranulate basophils when co-incubated, but not in response to enterotoxins that have no IgE response. Intracutaneous injection of SEB elicited mast cell degranulation in mice producing inflammatory responses but failed to produce a response in T cell deficient mice, indicating that both superantigens and T cells are required for mast cell degranulation.[28] Activated T cells induce degranulation and cytokine production by human mast cells after cell-to-cell contact.[29] Mast cells are usually not found in direct contact with T cells at inflammatory sites; consequently, IgE induction against staphylococcal superantigens by activated T cells might be the mechanism of mast cell degranulation. Additionally, staphylococcal superantigens and T cells together contribute in the synthesis of serum specific IgE to superantigens and *PTPN22* gene polymorphism may enhance this process.

CU has a complex physiopathology that involves multiple inflammatory pathways.[30] Autoantibodies are one of the prominent factors that cause CU; however, they are confined to a certain CU population.[31,32] No association of various autoantibodies with *PTPN22* in CU patients noted in the present study suggest that *PTPN22* might not be involved in the autoimmune mechanism of CU in the Korean population. It was also found that *PTPN22* gene polymorphism (1858C>T) was not associated with responses to ASST in Polish CU patients.[33] The findings suggest that the *PTPN22* gene polymorphism might not be involved in autoantibody mediated CU.

In conclusion, intronic polymorphisms of *PTPN22* at 20628A>G and 14943C>T enhances serum specific IgE responses to TSST-1 and SEA respectively, which may contribute to CU pathogenesis. Further studies are required to understand molecular genetic mechanisms by which *PTPN22* polymorphisms affect the production of serum specific IgE antibodies responses to staphylococcal superantigens.

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